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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/008,789	11/08/2001	C. Frank Bennett	RTS-0333	4716

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 02/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/008,789	BENNETT ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 2, 4-10, 12-15, and 19-22* is/are pending in the application.

4a) Of the above claim(s) *21 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4-10, 12-15, 19, and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicants Amendment and Remarks filed November 19, 2004.

Claims 1, 2, 4-10, 12-15, and 19-22 are pending. Claims 1 and 19 have been amended.

Claims 1, 2, 4-10, 12-15, 19, and 20 have been examined on the merits.

This application contains claims 21 and 22 drawn to an invention nonelected with traverse on August 27, 2002. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed August 19, 2004, claim 19 was rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. **This rejection is withdrawn** in view of Applicants amendment to the claim to recite SEQ ID NO:3 and SEQ ID NO:11.

Claim Rejections - 35 USC § 102

In the previous Office Action mailed August 19, 2004, claims 1, 2, 12, 14, 19, and 20 were rejected under 35 U.S.C. 102(b) as being anticipated by Murthy et al. (Journal of Biological Chemistry, 1999 Vol. 274:20679-20667). **This rejection is withdrawn** in view of Applicants amendment to the claim to recite "nucleobases 259 through 1586 of the coding region of a

nucleic acid molecule of SEQ ID NO:3". It is noted that Murthy et al. disclose a primer that is reverse complementary to nucleobases 169-148 of SEQ ID NO:3 of the instant invention.

In the previous Office Action mailed August 19, 2004, claims 1, 2, 12, 14, 19, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhao et al (Gene Expression, 1999 Vol. 8:207-217) [Applicants reference AE]. **This rejection is withdrawn** in view of Applicants amendment to the claim to recite "nucleobases 259 through 1586 of the coding region of a nucleic acid molecule of SEQ ID NO:3". It is noted that Zhao et al. disclose an upstream adaptor primer targeted to the 5' end of human Trip6.

In the previous Office Action mailed August 19, 2004, claims 1, 2, 12, 14, 19, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Yi et al. (Genomics, 1998 Vol. 49:314-316) [Applicants reference AD]. **This rejection is withdrawn** in view of Applicants amendment to the claim to recite "nucleobases 259 through 1586 of the coding region of a nucleic acid molecule of SEQ ID NO:3". It is noted that Yi et al. disclose an oligonucleotide primer that is reverse complementary to nucleobases 1689-1665 of SEQ ID NO:3 of the instant invention.

In the previous Office Action mailed August 19, 2004, claims 1, 2, 4-10, 12-15, 19, and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Cowsert et al. [U.S. Patent No. 6,492,173]. **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed August 19, 2004.

Response to Arguments

In response to this rejection, Applicants argue that the antisense oligonucleotide disclosed by Cowsert et al. is not complementary to bases 1518-1533 of SEQ ID NO:3, but rather has reverse identity with bases 1518-1533 of SEQ ID NO:3 of the instant invention. Applicants contend that the antisense oligonucleotide disclosed by Cowsert could not hybridize to bases 1518-1533 of SEQ ID NO:3, since the antisense oligonucleotide has reverse identity with bases 1518-1533 of SEQ ID NO:3 of the instant invention.

Applicant's arguments have been fully considered, but are not found persuasive. The Examiner is not clear what Applicants mean when saying that the antisense oligonucleotide disclosed by Cowsert et al. is not complementary to bases 1518-1533 of SEQ ID NO:3, but rather has reverse identity with bases 1518-1533 of SEQ ID NO:3 of the instant invention. The term "reverse identity" found in Applicants arguments is unclear to the Examiner as this is not an art-recognized term and the specification as filed does not lend any information as to what Applicants intend this term to mean.

It is noted that the instant specification at page 8, lines 12-37 recite:

"specifically hybridizable" and "complementary" are terms which are used to indicate a sufficient degree of complementarity or precise pairing such that stable and specific binding occurs between the oligonucleotide and the DNA or RNA target.

In the previous Office Action mailed August 19, 2004, the Examiner has provided a sequence search alignment showing that the antisense oligonucleotide disclosed by Cowsert et al. is clearly complementary to bases 1518-1533 of SEQ ID NO:3 of the instant invention. For clarity, the Examiner is providing this sequence search alignment below:

```
RESULT 745
AR266237/c
LOCUS       AR266237                 18 bp    DNA     linear   PAT 10-APR-2003
DEFINITION  Sequence 49 from patent US 6492173.
ACCESSION   AR266237
VERSION     AR266237.1  GI:29695083
KEYWORDS    .
SOURCE      Unknown.
  ORGANISM  Unknown.
            Unclassified.
REFERENCE   1  (bases 1 to 18)
  AUTHORS   Cowsert,L.M.
  TITLE     Antisense inhibition of cyclin D2 expression
  JOURNAL   Patent: US 6492173-A 49 10-DEC-2002;
FEATURES             Location/Qualifiers
     source          1. .18
                     /organism="unknown"
                     /mol_type="genomic DNA"

  Query Match             0.8%;  Score 14.4;  DB 1;  Length 18;
  Best Local Similarity   93.8%;  Pred. No. 6e+02;
  Matches   15;  Conservative    0;  Mismatches    1;  Indels    0;  Gaps    0;

Qy       1518 GCACATCTTGTGCAAG 1533
              ||||||||||| |||||
Db         17 GCACATCTTGCGCAAG 2
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The issue is would the antisense oligonucleotide disclosed by Cowsert et al. specifically hybridize to SEQ ID NO:3 of the instant invention. As discussed in the previous Office Action mailed August 19, 2004, at page 13, first full paragraph, it is noted that the complimentarity between the antisense oligonucleotide targeted to cyclin D2 disclosed by Cowsert et al. and nucleobases 1518-1533 of SEQ ID NO:3 is not contiguous as the local similarity is almost 94% and contains only one mismatch (see above sequence alignment). Given this high degree of similarity/complementarity, the antisense oligonucleotide disclosed by Cowsert et al. meets all the structural requirements of the instant claims and would be expected to specifically hybridize to a nucleic acid encoding thyroid hormone receptor interactor 6, as per applicant's definition set forth in the specification as filed, page 8 lines 12-37. For clarity page 8, lines 12-37 recite:

"specifically hybridizable" and "complementary" are terms which are used to indicate a sufficient degree of complementarity or precise pairing such that stable and specific binding occurs between the oligonucleotide and the DNA or RNA target. It is understood in the art that the sequence of an antisense compound need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable.

Therefore, the Examiner believes that the sequence search alignment clearly shows that the antisense oligonucleotide disclosed by Cowsert et al. is complementary to bases 1518-1533 of SEQ ID NO:3 of the instant invention. And, given this high degree of complementarity, the

antisense oligonucleotide disclosed by Cowsert et al. would specifically hybridize to SEQ ID NO:3, as per applicant's definition of "specifically hybridize" set forth in the specification as filed, pages 8 and 9.

In the previous Office Action mailed August 19, 2004, claims 1, 2, 4-10, 12, 15, 19, and 20 were rejected under 35 U.S.C. 103(a) as being unpatentable over Murthy et al. (Journal of Biological Chemistry, 1999 Vol. 274:20679-20667) in view of Milligan et al. (Journal of Medicinal Chemistry, 1993 Vol. 36:1923-1937), and further in view of Baracchini et al. [U.S. Patent No. 5801154] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288). **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed August 19, 2004.

Response to Arguments

In response to this rejection, Applicants argue that the claims have been amended to recite "nucleobases 259 through 1586 of the coding region of a nucleic acid molecule of SEQ ID NO:3 encoding thyroid hormone receptor interactor 6". Applicants contend that the combination of prior art references do not teach all the limitations of the claims, there is no motivation to modify the references or combine the teaching to produce the claimed invention, and a reasonable expectation of success has not been established.

First, Applicants argue that claim 1 has been amended to recite, "nucleobases 259 through 1586 of the coding region of a nucleic acid molecule of SEQ ID NO:3 encoding thyroid hormone receptor interactor 6". Applicants contend that the prior art references cited by the

Examiner do not teach or suggest the target site recited in claim 1 as amended. This argument has been considered but has not been found persuasive because nucleobases 259 through 1586 consist of the coding region of a nucleic acid encoding thyroid hormone receptor interactor 6 (SEQ ID NO:3). Given this proviso, the skilled artisan would be motivated to target the coding region of a known target gene, as taught by Baracchini et al. (see column 9, lines 6-67 and column 10, lines 1-25).

Second, Applicants argue that the combination of art cited by the Examiner fails to render obvious the rejected claims because the references at best contain a generalized incentive to make antisense molecules against thyroid hormone receptor interactor 6, based on the discovery and characterization of thyroid hormone receptor interactor 6 protein as taught by Murthy et al. and a generalized teaching to make antisense targeted to a "causative gene" as taught by Milligan et al. Applicants argue that the cited combination of art at best provides only a generalized incentive to make antisense compounds against thyroid hormone receptor interactor 6. Applicants further contend that the cited combination of prior art provides no teaching or suggestion to make specific antisense compounds. This argument has been considered but has not been found persuasive because Murthy et al. identify the structural domains of thyroid hormone receptor interactor 6 (also called ZRP-1), including the 5'-untranslated region, the start codon region, **the coding region**, or the 3'-untranslated region, and the region(s) involved in protein-protein interactions. Further, Murthy et al. also teach that the identification of other protein interacting domains is required for a better understanding of the role of ZRP-1 in cellular function. Milligan teach antisense techniques as a tool for probing the functions of individual genes. Milligan et al. further teach making an antisense oligonucleotide if the mRNA sequence

(or cDNA) is known. Therefore, it would have been obvious to one of skill in the art to make the antisense oligonucleotides of the instant invention using the ZRP-1 sequence taught by Murthy et al. and following the method of Milligan et al. One skilled in the art would be motivated to make antisense targeted to thyroid hormone receptor interactor 6 to probe the function of thyroid hormone receptor interactor 6 in cellular processes. One of skill in the art would have been motivated to make antisense targeted to nucleobases 259 through 1586 of the coding region of a nucleic acid molecule of SEQ ID NO:3 encoding thyroid hormone receptor interactor 6 because nucleobases 259 through 1586 consist of the coding region of thyroid hormone receptor interactor 6 and Baracchini et al. teach making antisense to different regions (e.g. 5'-untranslated region, the start codon region, the coding region, or the 3'-untranslated region) of a known gene (see column 9, lines 6-67 and column 10, lines 1-25).

Third, Applicants argue that modifying or combining art to make out a prima facie case of obviousness requires that the prior art provide an ordinarily skilled artisan with a reasonable expectation of success in making the claimed invention. Applicants rely on MPEP 2143.02. Applicants contend that the cited references fail to provide a reasonable expectation of success. Applicants argue that the review of randomly chosen patents issued to the assignee which revealed that each and every patent contained anywhere from a few to many oligonucleotides that inhibit target gene expression, as discussed in the previous Office Action mailed August 19, 2004, do not contain oligonucleotides that inhibit encoding thyroid hormone receptor interactor 6. Applicants contend that these patents do not provide any direction as to which of the many possible choices was likely to be successful when targeting nucleobases 259 through 1586 for the coding region of a nucleic acid molecule encoding thyroid hormone receptor interactor 6. This

argument has been considered but is not found persuasive because the review was relied upon to depict the true expectation of success of making antisense oligonucleotides to known target genes that inhibit gene expression. Although the patents are not directed to a nucleic acid molecule encoding thyroid hormone receptor interactor 6, the disclosure and teachings contained within these patents provides a clear expectation of making antisense oligonucleotides to different regions, including the coding region, of known target genes, that inhibit gene expression. Therefore, one of ordinary skill in the art would have expected success in making an antisense compound targeting to nucleobases 259 through 1586 for the coding region of a nucleic acid molecule encoding thyroid hormone receptor interactor 6 using the sequence taught by Murthy et al. and following the motivation of Milligan et al. and the methods of Baracchini et al.

Accordingly, Applicants arguments have not been found persuasive.

Applicant's amendment necessitated the new ground(s) of rejection presented below:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-10, 12-15, 19, and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The amendment filed November 19, 2004 introduces new matter into the disclosure because it recites the limitation, "nucleobases 259 through 1586 of the coding region of a nucleic acid molecule of SEQ ID NO:3 encoding thyroid hormone receptor interactor 6" in claim 1. There is no support in the instant specification as filed for "nucleobases 259 through 1586 of the coding region of a nucleic acid molecule of SEQ ID NO:3 encoding thyroid hormone receptor interactor 6". The response filed November 19, 2004 indicates that support for the limitation is present in Table 1 at SEQ ID NOs: 15-67. It is noted that Table 1, SEQ ID NOs: 15-67 shows several dozen specific antisense oligonucleotide targeted to different parts of the coding region of a nucleic acid molecule encoding thyroid hormone receptor interactor 6 (SEQ ID NO:3). However, Table 1 does not have support for "nucleobases 259 through 1586 of the coding region of a nucleic acid molecule of SEQ ID NO:3 encoding thyroid hormone receptor interactor 6" because there are large gaps between the targeting regions within the coding region. For example, see SEQ ID NOs: 15 and 16 and SEQ ID NOs: 23 and 24. Therefore the limitation "nucleobases 259 through 1586 of the coding region of a nucleic acid molecule of SEQ ID NO:3 encoding thyroid hormone receptor interactor 6" is new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (571) 272-0758. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
January 28, 2005

JOHN L. LeGUYADER
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